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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/709,045	11/10/2000	M. Rigdon Lentz	LEN 102	3239

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EXAMINER	
SEHARASEYON, JEGATHEESAN	
ART UNIT	**PAPER NUMBER**
1647	

DATE MAILED: 02/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/709,045	LENTZ, M. RIGDON	
	Examiner	Art Unit	
	Jegatheesan Seharaseyon	1647	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 October 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,5,6,8-11 and 17-22* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 5, 6, 8-11 and 17-22* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *10/06/2003*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

1. This office action is in response to the amendment and response filed on 10/30/03. Claims 1-3, 5, 6, 8-11 and 17–22 are under consideration.

2. Applicant has provided a copy of the declaration filed in U. S. S. N. 09/444, 144.

Claim Rejections - 35 USC § 103, maintained

3. Claims 1-3, 6, 8-11 and 17-22 are rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (6,017,527) is maintained for reasons of record of Office Action of July 29, 2003 page 3. Applicant's arguments and declaration, filed 10/30/03, with respect to rejection of claims 1-3, 6, 8-11 and 17–22 has been considered fully but is not persuasive.

Applicant argues that Lentz reference teaches away from the selective removal of soluble cytokine receptor molecules. Applicant further asserts that molecular weight cut off for the selectivity is approximately 200,000 daltons. However, the reference uses a second filter, which has a molecular weight, cut off of 30,000 daltons (column 4, lines 33-50). Therefore, removing the soluble TNF receptor. Lentz reference was used to a method and system for removing diseased tissue from the blood of a patient for treating diseases and conditions such as cancer and returning the treated blood to the patient to initiate an immune response (see abstract). Lentz also teaches that the method can treat cancer (including solid tumors) and other diseases including the virally induced AIDS (see column 2, lines 45-50). Lentz also contemplates the separation of plasma prior to ultrafiltration and returning the treated plasma and blood to the patient (see

column 10, lines 1-10). Lentz reference was not introduced to discuss the inhibitors involved in the immunosuppression of anti-tumor response. Furthermore, one cannot show non obviousness by attacking references individually where the rejections are based on combination of references (See *In re Keller*, 642 F.2d 413, 208 USPQ 871 (CCPA 1981); *In re Merck & Co.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986)). It is the combined teachings of the references that would have suggested to those of ordinary skill in the art.

Applicant argues Selinksky separately, by stating that this reference in no way makes obvious the removal of sTNFR to treat tumors or other disorders. Furthermore, Applicant citing the declaration of Howell et al. state that "although the statement in Selinsky et al. may cause one of skill in the art to consider how to antagonize or remove sTNFRI *in situ*, such a statement is merely an invitation to experimentation and opens the door for one of skill in the art to consider wide range of possible approaches". Contrary to Applicants and assertion and the declaration, the Selinsky reference teaches the following: Soluble tumor necrosis factor receptor type I (sTNFRI) is a potential inhibitor of TNF with the potential to suppress a variety of effector mechanisms important in tumor immunity. In addition, it states that sTNFRI influences tumor survival *in vivo* is suggested by results from human clinical trials of Ultraphoresis (summary, page: 88). Thus, providing a reasonable expectation of success to remove the cytokine from the transformed, infected or diseased tissue.

As discussed in the Office Action of July 29, 2003, Van Zee et al. reference was introduced to teach the antibodies to both sTNFRI and sTNFRII receptors. Though

Applicant asserts that the instant claims are directed to a method of "increasing inflammation and the immune response against tumors by removing sTNFR" there is no such recitation the claims. The observation by Van Zee et al. that the sTNF receptors bind to TNF-α does not contradict any of the facts of the instant invention and does not teach away from what is claimed. Infact in the instant invention antibodies prevent soluble cytokine receptor from binding to the cytokine.

Applicant does concede that Maraskovy et al. teach that one can use an antibody column to remove materials from the blood. However, Applicant contends that there is no teaching that it can be used to remove cytokine inhibitors to kill tumor cells. Maraskovy et al. reference was included to teach antibodies immobilized on beads for removal of antigens from blood sample. That is, to use immunoaffinity columns to separate cytokines, antigen-antibody complexes and activated cells. Therefore, contrary to Applicants assertion that the claims are allowable over Selinsky, VanZee, Lentz and Maraskovy it would have been *prima facie* obvious to one of ordinary skill in the art at the time the claimed invention was made to have used the method of Selinsky et al. to remove cytokine receptors using antibodies to the cytokine receptors (TNFR I and TNFR II, see Selinsky et al. and Van Zee et al) that inhibit immune response as taught by Lentz for removing diseased tissue to treat cancer and other virally induced diseases, from the blood of a patient with immobilizing the antibodies to the beads to remove the soluble cytokine receptors as taught by Maraskovsky et al.

In addition, one of ordinary skill in the art would have been motivated to with reasonable expectation of success in combining the teachings of Selinsky et al., Van

Zee et al., Lentz and Maraskovsky et al. because Selinsky et al. declare that "We, therefore, propose the development of methods and /or reagents capable of specifically removing sTNFR I, or antagonizing its effects *in situ,* as unconventional, yet promising, strategies for cancer immunotherapy." (see page 92). Moreover, one of ordinary skill in the art would have been motivated to and had a reasonable expectation of success in combining the teachings of Selinsky et al., Lentz and Maraskovsky et al. because Maraskovsky et al. teach antibodies immobilized on beads for removal of antigens from blood sample. In addition, it would have been obvious to use either a polyclonal antibody or a monoclonal antibody as well as a panel of antibodies that are specific for either one immune system or several immune system inhibitors, for Lentz teaches that there are immunosuppressive components in blood that are separated by Ultrfiltration to boost the immune system. In addition, one skilled in the art would know to remove the antibody/antigen complex prior to administering the biological fluid to the patient. Thus, it would have been obvious to use the method of Maraskovsky et al. to immobilize an antibody of Selinsky or Van Zee which specifically binds the sTNFR I or sTNFR II, wherein the sTNFR I or sTNFR II inhibits the immune response, and is removed in the method of Lentz using an immobilized antibody. Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references. Thus, the rejection is maintained.

4. Claim 5 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of

Maraskovsky et al (6,017,527) and Feinman et al. (1987) is maintained for reasons of record of Office Action of July 29, 2003 page 7.

Applicant's arguments and declaration, filed 10/30/03, with respect to rejection of claim 5 has been considered fully but not persuasive. The relevance of Selinsky et al., Van Zee et al., Lentz and Maraskovsky et al. has been set forth above in paragraph 4 and response of July 29, 2003 paragraph 11a. However, the references did not explicitly recite the use of other compounds/agents for the treatment of cancer tissue by the use of cytokines. Feinman et al. discloses the use of interferon-γ (a cytokine) to increase monocyte cytotoxicity by sensitizing target cells to the lytic action of TNF (see abstract). Applicant asserts that Feinman reference does not make up for the deficiencies of the references. Further it is alleged that Feinman reference is not drawn to an *in vivo* situation, nor to treatment of tumor cells. Contrary to Applicants allegation, Feinman use A673 a human rhabdomyosarcoma cell line and HT-29 a human colon adenocarcinoma cell line for the interferon study. Furthermore, there is a reasonable expectation that these studies can be replicated *in vivo.* Therefore, the invention as a whole would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made, as evidenced by the references. Thus, the rejection of claim 5 under 35 USC § 103 as being unpatentable over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (6,017,527) and Feinman et al. (1987) is maintained.

5. Claim 10 is rejected under 35 U.S.C. 103(a) as being unpatentable over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (6,017,527) and Goodman et al. (5,817,522) is maintained for reasons of record of Office Action of July 29, 2003 page 8.

Applicant's arguments and declaration, filed 10/30/03, with respect to rejection of claim 10 under 35 USC § 103 as being unpatentable over has been considered fully but not persuasive. The relevance of Selinsky et al., Van Zee et al., Lentz and Maraskovsky et al. has been set forth above in paragraph 4 and response of July 29, 2003 paragraph 11a. However, the references did not explicitly recite the use of humanized antibody. Goodman et al. disclose several antibodies including humanized antibodies (column 11, lines 52-65). It is asserted by the Applicant that the Office has characterized the claims inaccurately in that it does recite treating whole blood, but treating whole blood or plasma. However, claim 1 of the instant invention reads ".....contacting the blood of a patient....". Thus, it is unclear where the recitation of whole blood or plasma is recited in the instant claims. Applicant concedes that Goodman reference does teach the making of humanized antibodies. However, it is alleged that it does not make up for the deficiencies of the other references and dose not provide the motivation because the antibodies described by Goodman et al. are immobilized. While it is true that Goodman et al. describes immobilized antibodies, the reference is not limited to only immobilized antibodies. Goodman et al. reference was introduced to teach the use of humanized antibodies as anti-ligand. Thus, one having ordinary skill in the art would have been motivated to use humanized antibodies to the receptor to remove the soluble receptors

from the patient. Therefore, the rejection of claim 10 as obvious over Selinsky et al. (1998) and Van Zee et al. (1992) in view of Lentz (4,708,713) and further in view of Maraskovsky et al (U.S. Patent (6,017,527) and Goodman et al (U.S. Patent 5,817,522) is maintained.

Double Patenting rejection maintained

6. Claims 1-3, 5, 6 and 8-11 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1, 2 and 5-8 of U.S. Patent No. 6,231,536.

Applicants arguments have been fully considered but are not deemed persuasive. Applicants argue that the Office has not properly applied the analysis between the Patent and the instant Application. Further, Applicant contends that the claims of U.S. Patent No. 6, 231,536 were interpreted by the Office, as requiring the removal of the soluble tissue necrosis factor using molecular weight exclusion. This point was clarified in the Office Action mailed 7/29/03 as directed to the removing of soluble cytokine receptor molecules by using an antibody that binds to the soluble cytokine receptor molecules from blood (see claims 5-8). Thus the broad claims generically read on the instant invention. Thus the rejection of claims of claims 1-3, 5, 6 and 8-11 are maintained.

7. New grounds of rejection.

New Double Patenting rejection

8. Claims 1-3, 5, 6, 8-11 and 17-22 are provisionally rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 8-10, 12 and 16-20 of copending Application No. 09/699, 003. Although the conflicting claims are not identical, they are not patentably distinct from each other because the instant invention is directed to reducing the amount of transformed, infected or diseased tissue and prevents the soluble cytokine receptor from binding to the cytokine, until the transformed, infected, or diseased tissue is reduced in amount. The copending Application No. 09/699, 003, recite claims that encompass the instant invention. Specifically, the method describes inducing an immune response against transformed, infected or diseased tissue comprising selectively removing soluble cytokine receptor molecules until the transformed, infected, or diseased tissue is reduced in amount. The applications use ultrapheresis to remove soluble cytokine receptors to stimulate the patient's immune system to attack solid tumors. Therefore, the broad claims generically read on the instant invention.

It would have been *prima facie* obvious to one of ordinary skill in the art, at the time the invention was made, to modify the method described in the copending Application No. 09/699, 003 to remove other soluble cytokine receptor (sTNFR-I and sTNFR-II) molecules to induce an immune response. One skilled in the art, at the time the invention was made to would have been motivated to substitute molecules which will bind sTNFR-I and sTNFR-II receptor molecules to enhance the immune response.

Thus, claims 1-3, 5, 6, 8-11 and 17-22 of the instant application are obvious over claims 1-5, 8-10, 12 and 16-20 of copending Application No. 09/699, 003.

This is a provisional obviousness-type double patenting rejection because the conflicting claims have not in fact been patented.

Interference

9. Interference has not been declared because there are pending issues in the instant application and no allowable subject matter..

10. No claims are allowable.

Contact information

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jegatheesan Seharaseyon whose telephone number is 571-272-0892. The examiner can normally be reached on M-F: 8:30-4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Kunz can be reached on 571-272-0887. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

JS

Lorraine Spector

LORRAINE SPECTOR
PRIMARY EXAMINER